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# Harrison's PRINCIPLES of INTERNAL MEDICINE

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pointed out above, criteria for clearly identifying such patients do not yet exist.

Gene transfer therapy has the potential to provide marked improvement in or cure of patients with sickle cell disease while avoiding some of the risks of allogeneic transplantation. There was considerable optimism about this approach in the early 1980s. However, it is now apparent that for several reasons the difficulties in implementing gene therapy for sickle cell disease are much greater than those encountered in the treatment of enzyme defects such as adenosine deaminase deficiency, where gene transfer has been performed with some modest success. In sickle cell disease, the clinical manifestations are caused by the functioning of the abnormal gene, and merely placing a normal gene into the hematopoietic stem cell does not prevent the formation of sickle hemoglobin. Moreover, to be effective it is necessary for the transduced gene not only to function but to function at a very high level. The rate at which hemoglobin is normally synthesized is several orders of magnitude higher than that of most other proteins. Finally, it has been difficult to maintain continuing expression of genes transduced into primate hematopoietic stem cells. Prolonged activity would be essential for gene transfer therapy to be successful in sickle cell disease.

**HEMOGLOBIN C DISORDERS** The most important clinical consequence of the hemoglobin C mutation is its interaction with the sickle mutation to cause hemoglobin SC disease, a form of sickle cell disease, as discussed above. Hemoglobin C trait is asymptomatic, and hemoglobin CC disease, the homozygous state, causes a mild anemia characterized by target-shaped, flattened, and sometimes folded erythrocytes. Characteristic intraerythrocytic crystals can sometimes be found, but the diagnosis of this disorder depends upon hemoglobin electrophoresis. A patient with manifestations of sickle cell disease who has splenomegaly and whose erythrocytes are target cells is likely to have SC disease.

**HEMOGLOBIN E DISORDERS** The hemoglobin E mutation produces an amino acid substitution, 26Glu→Lys, through a G→A mutation in the 79th nucleotide of the coding sequence of the cDNA. It is unusual in that some of the mRNA bearing this mutation is spliced abnormally because of the substitution, and because the abnormally spliced message cannot be translated into globin, there is a marked β-globin deficiency. As a result, the hemoglobin E mutations cause a thalassemia-like state. Hemoglobin E trait is characterized by the presence of target cells, hypochromia, microcytosis, and mild anemia. The homozygous state for hemoglobin E is also clinically mild, with striking microcytosis usually without splenomegaly. The β thalassemia/hemoglobin E compound heterozygote has a somewhat more severe presentation than homozygous hemoglobin E disease; splenomegaly is usually present.

**UNSTABLE HEMOGLOBINS** Some mutations cause the formation of unstable hemoglobin molecules that precipitate in vivo, causing hemolytic anemia. Most of these mutations affect the binding of heme by globin or the intermolecular contacts between the globin chain in the tetramer. A single copy of a gene for an unstable hemoglobin is sufficient to cause hemolytic disease, and thus these hemoglobinopathies are inherited as autosomal dominant disorders. Hemoglobins Geneva and Köln are examples. Hemolysis varies greatly in severity and may be accentuated by the ingestion of "oxidative" drugs, such as those that cause hemolysis in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency (see Chap. 109). Sulfonamides have been the chief offending agents. Heinz bodies, particles of denatured protein adhering to the cell membrane, are usually seen in patients who have been splenectomized.

Although unstable hemoglobins may be electrophoretically abnormal, they are best detected by the isopropanol stability test. In recent years a thalassemia-like state inherited as a dominant disorder and designated as a *hyperunstable hemoglobin syndrome* has been delineated. Here, the hemoglobin is so unstable that none of it can be detected in red cells. Instead, the diagnosis must be established by showing a defect in the globin gene by DNA analysis. Even though only one of the copies of the β chain is abnormal, the very unstable hemoglobin apparently damages the erythrocytes sufficiently that severe hemolytic anemia occurs.

**HEMOGLOBINS WITH ABNORMAL OXYGEN AFFINITY** The steady-state level of hemoglobin is presumably maintained by an as yet uncharacterized oxygen sensor. When an abnormal hemoglobin binds oxygen too tightly (i.e., has an increased oxygen affinity), the sensor causes more erythropoietin to be released. Consequently, the red cell mass increases. Patients with such mutations may become sufficiently polycythemic so as to require periodic phlebotomies. High-affinity hemoglobins are commonly also unstable, so that a compensated hemolytic state with a normal hemoglobin level results. Hemoglobins Zürich and Yakima are examples. Conversely, mutant hemoglobins with a decreased oxygen affinity cause a mild, usually asymptomatic anemia. Hemoglobin Kansas is an example.

These hemoglobinopathies are diagnosed by determining the oxygen dissociation of the hemoglobin freed of 2,3-BPG. This compound must be removed to distinguish high- and low-affinity hemoglobins from hereditary metabolic disorders of the red cell such as phosphofructokinase deficiency, which causes polycythemia by lowering the 2,3-BPG level, or pyruvate kinase deficiency, which increases the red cell 2,3-BPG level. Like the hemoglobinopathies caused by the unstable hemoglobins, the clinical syndromes caused by these mutant hemoglobins are inherited in an autosomal dominant fashion.

## THE THALASSEMIAS

The thalassemias are divided into the α thalassemias, in which it is the production of α globin that is deficient, and the β thalassemias, in which β globin production is defective.

**THE α THALASSEMIAS** **Pathophysiology** α Thalassemias result in an excess production of β chains in adults and children and γ chains in newborns. The β chains that accumulate form tetramers—hemoglobin Barts ($\gamma_4$) in infants and hemoglobin H ($\beta_4$) in adults. These tetramers are abnormal hemoglobins with marked instability, a left-shifted oxygen dissociation curve with a lack of cooperativity, i.e., the normal sigmoid shape. The hematologic manifestations of the α thalassemias are a function principally of the extent to which these abnormal tetramers accumulate. This, in turn, depends upon how many of the four α loci have been deleted or inactivated by a mutation, as indicated below.

**Clinical Manifestations** (Table 107-4) *Deletion or mutation of all four α loci* Deletion of all of the α-globin genes is the most catastrophic form of α thalassemia. It is incompatible with extrauterine life, and the infants are either dead at birth with hydrops fetalis or die shortly after birth. They are severely edematous and have little circulating hemoglobin, which is almost entirely hemoglobin Barts.

*Deletion or mutation of three of the four α loci* Hemoglobin H disease results from deletion of all but one of the α-globin genes. The disorder resembles an unstable hemoglobinopathy, because both hemoglobin Barts and hemoglobin H are, in fact, unstable hemoglobins. Patients have a microcytic hypochromic anemia with target cells and Heinz bodies on the blood smear. Onset may be apparent during childhood, but in milder cases it is often not until adult life. Hemolytic anemia with marked splenomegaly is the characteristic presentation. Reticulocytes are increased.

*Deletion or mutation of two of the four α loci* Two α loci are sufficient for nearly normal erythropoiesis. This state has been called *α-thalassemia trait* and is characterized by mild anemia and moderate microcytosis and hypochromia. The hemoglobin concentration is usually within 10 or 20 g/L (1 or 2 g/dL) of normal, and the mean corpuscular volume (MCV) is in the 70 to 80 fL range. Because of the extraordinarily high prevalence (~30 percent) of deletion of one of the two α-globin loci on chromosomes of people of African origin, the inheritance of two such chromosomes is very common. This condition is very commonly mistaken for iron deficiency and treated inappropriately with iron.